US008895073B2

(12) **United States Patent**
Boyan et al.

(10) **Patent No.: US 8,895,073 B2**
(45) **Date of Patent: *Nov. 25, 2014**

(54) **HYDROGEL IMPLANT WITH SUPERFICIAL PORES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 866 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/052,826**

(22) Filed: **Mar. 21, 2011**

(65) **Prior Publication Data**

US 2011/0172771 A1 Jul. 14, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/053,409, filed on Feb. 7, 2005, now Pat. No. 7,910,124.

(60) Provisional application No. 60/542,389, filed on Feb. 6, 2004.

(51) **Int. Cl.**

A61K 9/50	(2006.01)
A61L 27/56	(2006.01)
A61F 2/44	(2006.01)
A61L 27/52	(2006.01)
A61F 2/30	(2006.01)

(52) **U.S. Cl.**

CPC ***A61L 27/56*** (2013.01); ***A61F 2/442*** (2013.01); ***A61L 27/52*** (2013.01); *A61F 2/3094* (2013.01); *A61F 2002/30011* (2013.01); *A61F 2002/30014* (2013.01); *A61F 2002/30784* (2013.01); *A61F 2250/0018* (2013.01); *A61F 2250/0023* (2013.01); *A61L 2430/38* (2013.01)

USPC **424/497**; 424/498

(58) **Field of Classification Search**

CPC .. A61K 9/5026; A61K 9/5031; A61L 31/145; A61L 27/56

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,276,996 A 10/1966 Lazare
3,663,470 A 5/1972 Nishimura et al.

(Continued)

FOREIGN PATENT DOCUMENTS

DE 20218703 U1 3/2003
EP 0222404 A1 5/1987

(Continued)

OTHER PUBLICATIONS

International Search Report for Application No. PCT/US2005/03899 mailed Jul. 15, 2008 (PCT/US2005/03899 is the corresponding PCT application of U.S. Appl. No. 11/053,410).

(Continued)

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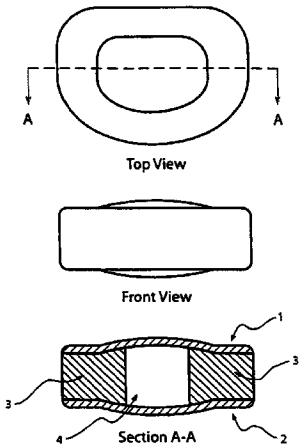
(57) **ABSTRACT**

Implantable biomaterials, particularly hydrogel substrates with porous surfaces, and methods for enhancing the compatibility of biomaterials with living tissue, and for causing physical attachment between biomaterials and living tissues are provided. Also provided are implants suitable for load-bearing surfaces in hard tissue repair, replacement, or augmentation, and to methods of their use. One embodiment of the invention relates to an implantable spinal disc prosthesis.

18 Claims, 2 Drawing Sheets



(56) **References Cited**

U.S. PATENT DOCUMENTS

3,673,612 A 7/1972 Merrill et al.
3,849,238 A 11/1974 Gould et al.
3,859,421 A 1/1975 Hucke
4,083,906 A 4/1978 Schindler et al.
4,205,400 A 6/1980 Shen et al.
4,351,069 A 9/1982 Ballintyn et al.
4,472,542 A 9/1984 Nambu
4,517,295 A 5/1985 Bracke et al.
4,524,064 A 6/1985 Nambu
4,609,337 A 9/1986 Wichterle et al.
4,663,358 A 5/1987 Hyon et al.
4,664,857 A 5/1987 Nambu
4,693,939 A 9/1987 Ofstead
4,731,081 A 3/1988 Tiffany et al.
4,734,097 A 3/1988 Tanabe et al.
4,738,255 A 4/1988 Goble et al.
4,753,761 A 6/1988 Suzuki
4,759,766 A 7/1988 Buttner-Janz et al.
4,772,284 A 9/1988 Jefferies et al.
4,784,990 A 11/1988 Nimrod et al.
4,787,905 A 11/1988 Loi
4,808,353 A 2/1989 Nambu et al.
4,828,493 A 5/1989 Nambu et al.
4,851,168 A 7/1989 Graiver et al.
4,911,720 A 3/1990 Collier
4,916,170 A 4/1990 Nambu
4,988,761 A 1/1991 Ikada et al.
4,995,882 A 2/1991 Destouet et al.
5,047,055 A 9/1991 Bao et al.
5,080,674 A 1/1992 Jacobs et al.
5,095,037 A 3/1992 Iwamitsu et al.
5,106,743 A 4/1992 Franzblau et al.
5,106,876 A 4/1992 Kawamura
5,108,428 A 4/1992 Capecchi et al.
5,108,436 A 4/1992 Chu et al.
5,118,667 A 6/1992 Adams et al.
5,141,973 A 8/1992 Kobayashi et al.
5,171,322 A 12/1992 Kenny
5,171,574 A 12/1992 Kuberasampath et al.
5,192,326 A 3/1993 Bao et al.
5,206,023 A 4/1993 Hunziker
5,219,360 A 6/1993 Georgiade
5,234,456 A 8/1993 Silvestrini
5,244,799 A 9/1993 Anderson
5,258,023 A 11/1993 Reger
5,258,042 A 11/1993 Mehta
5,258,043 A 11/1993 Stone
5,260,066 A 11/1993 Wood et al.
5,287,857 A 2/1994 Mann
5,288,503 A 2/1994 Wood et al.
5,290,494 A 3/1994 Coombes et al.
5,314,477 A 5/1994 Marnay
5,314,478 A 5/1994 Oka et al.
5,326,364 A 7/1994 Clift, Jr. et al.
5,336,551 A 8/1994 Gravier et al.
5,336,767 A 8/1994 Della Valle et al.
5,343,877 A 9/1994 Park
5,344,459 A 9/1994 Swartz
5,346,935 A 9/1994 Suzuki et al.
5,397,572 A 3/1995 Coombes et al.
5,399,591 A 3/1995 Smith et al.
5,401,269 A 3/1995 Buttner-Janz et al.
5,409,904 A 4/1995 Hecht et al.
5,410,016 A 4/1995 Hubbell et al.
5,442,053 A 8/1995 Della Valle et al.
5,458,643 A 10/1995 Oka et al.
5,458,645 A 10/1995 Bertin
5,489,310 A 2/1996 Mikhail
5,490,962 A 2/1996 Cima et al.
5,492,697 A 2/1996 Boyan et al.
5,494,940 A 2/1996 Unger et al.
5,502,082 A 3/1996 Unger et al.
5,512,475 A 4/1996 Naughton et al.
5,522,898 A 6/1996 Bao
5,534,028 A 7/1996 Bao et al.
5,541,234 A 7/1996 Unger et al.
5,545,229 A 8/1996 Parsons et al.
5,556,429 A 9/1996 Felt
5,556,431 A 9/1996 Buttner-Janz
5,578,217 A 11/1996 Unger et al.
5,626,861 A 5/1997 Laurencin et al.
5,645,592 A 7/1997 Nicolais et al.
5,656,450 A 8/1997 Boyan et al.
5,658,329 A 8/1997 Purkait
5,674,241 A 10/1997 Bley et al.
5,674,295 A 10/1997 Ray et al.
5,674,296 A 10/1997 Bryan et al.
5,688,459 A 11/1997 Mao et al.
5,700,289 A 12/1997 Breitbart et al.
5,705,780 A 1/1998 Bao
5,716,416 A 2/1998 Lin
5,750,585 A 5/1998 Park et al.
5,766,618 A 6/1998 Laurencin et al.
5,769,897 A 6/1998 Harle
5,789,464 A 8/1998 Muller
5,795,353 A 8/1998 Felt
5,824,093 A 10/1998 Ray et al.
5,824,094 A 10/1998 Serhan et al.
5,844,016 A 12/1998 Sawhney et al.
5,847,046 A 12/1998 Jiang et al.
5,855,610 A 1/1999 Vacanti et al.
5,863,297 A 1/1999 Walter et al.
5,863,551 A 1/1999 Woerly
5,876,452 A 3/1999 Anthanasiou et al.
5,876,741 A 3/1999 Ron
5,880,216 A 3/1999 Tanihara et al.
5,900,245 A 5/1999 Sawhney et al.
5,916,585 A 6/1999 Cook et al.
5,925,626 A 7/1999 Della Valle et al.
5,928,239 A 7/1999 Mirza
5,935,129 A 8/1999 McDevitt et al.
5,944,754 A 8/1999 Vacanti
5,947,844 A 9/1999 Shimosaka et al.
5,948,829 A 9/1999 Wallajapet et al.
5,957,787 A 9/1999 Hwang
5,976,186 A 11/1999 Bao et al.
5,981,826 A 11/1999 Ku et al.
6,001,352 A 12/1999 Boyan et al.
6,027,744 A 2/2000 Vacanti et al.
6,060,534 A 5/2000 Ronan et al.
6,093,205 A 7/2000 McLeod et al.
6,102,954 A 8/2000 Albrektsson et al.
6,103,255 A 8/2000 Levene et al.
6,132,465 A 10/2000 Ray et al.
6,156,067 A 12/2000 Bryan et al.
6,171,610 B1 1/2001 Vacanti et al.
6,187,329 B1 2/2001 Agrawal et al.
6,206,927 B1 3/2001 Fell
6,224,630 B1 5/2001 Bao et al.
6,231,605 B1 5/2001 Ku
6,255,359 B1 7/2001 Agrawal et al.
6,264,695 B1 7/2001 Stoy
6,268,405 B1 7/2001 Yao et al.
6,271,278 B1 8/2001 Park et al.
6,280,475 B1 8/2001 Bao et al.
6,337,198 B1 1/2002 Levene et al.
6,340,369 B1 1/2002 Ferree
6,341,952 B2 1/2002 Gaylo et al.
6,344,058 B1 2/2002 Ferree
6,355,699 B1 3/2002 Vyakarnam et al.
6,358,251 B1 3/2002 Mirza
6,371,984 B1 4/2002 Van Dyke et al.
6,376,573 B1 4/2002 White et al.
6,379,962 B1 4/2002 Holy et al.
6,383,519 B1 5/2002 Sapieszko et al.
6,402,784 B1 6/2002 Wardlaw
6,402,785 B1 6/2002 Zdeblick et al.
6,419,704 B1 7/2002 Ferree
6,428,576 B1 8/2002 Haldimann
6,451,059 B1 9/2002 Janas et al.
6,472,210 B1 10/2002 Holy et al.
6,482,234 B1 11/2002 Weber et al.
6,531,523 B1 3/2003 Davankov et al.
6,533,818 B1 3/2003 Weber et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,534,084 B1 3/2003 Vyakarnam et al.
6,558,421 B1 5/2003 Fell et al.
6,602,291 B1 8/2003 Ray et al.
6,607,558 B2 8/2003 Kuras
6,610,094 B2 8/2003 Husson
6,629,997 B2 10/2003 Mansmann
6,645,248 B2 11/2003 Casutt
6,667,049 B2 12/2003 Janas et al.
6,686,437 B2 2/2004 Buchman et al.
6,707,558 B2 3/2004 Bennett
6,710,126 B1 3/2004 Hirt et al.
6,726,721 B2 4/2004 Stoy et al.
6,733,533 B1 5/2004 Lozier
6,734,000 B2 5/2004 Chin et al.
6,740,118 B2 5/2004 Eisermann et al.
6,773,713 B2 8/2004 Bonassar et al.
6,783,546 B2 8/2004 Zucherman et al.
6,800,298 B1 10/2004 Burdick et al.
6,802,863 B2 10/2004 Lawson et al.
6,827,743 B2 12/2004 Eisermann et al.
6,840,960 B2 1/2005 Bubb
6,849,092 B2 2/2005 Van Dyke et al.
6,855,743 B1 2/2005 Gvozdic
6,875,232 B2 4/2005 Nigam
6,875,386 B1 4/2005 Ward et al.
6,875,442 B2 4/2005 Holy et al.
6,878,384 B2 4/2005 Cruise et al.
6,881,228 B2 4/2005 Zdeblick et al.
6,893,463 B2 5/2005 Fell
6,893,466 B2 5/2005 Trieu
6,923,811 B1 8/2005 Carl et al.
6,960,617 B2 11/2005 Omidian et al.
6,982,298 B2 1/2006 Calabro et al.
6,993,406 B1 1/2006 Cesarano, III et al.
7,008,635 B1 3/2006 Coury et al.
7,012,034 B2 3/2006 Heide et al.
7,022,522 B2 4/2006 Guan et al.
7,048,766 B2 5/2006 Ferree
7,052,515 B2 5/2006 Simonson
7,060,097 B2 6/2006 Fraser et al.
7,066,958 B2 6/2006 Ferree
7,066,960 B1 6/2006 Dickman
7,083,649 B2 8/2006 Zucherman et al.
7,091,191 B2 8/2006 Laredo et al.
7,156,877 B2 1/2007 Lotz et al.
7,186,419 B2 3/2007 Petersen
7,201,774 B2 4/2007 Ferree
7,201,776 B2 4/2007 Ferree et al.
7,214,245 B1 5/2007 Marcolongo et al.
7,217,294 B2 5/2007 Kusanagi et al.
7,235,592 B2 6/2007 Muratoglu et al.
7,250,060 B2 7/2007 Trieu
7,258,692 B2 8/2007 Thelen et al.
7,264,634 B2 9/2007 Schmieding
7,282,165 B2 10/2007 Williams, III et al.
7,291,169 B2 11/2007 Hodorek
7,316,919 B2 1/2008 Childs et al.
7,332,117 B2 2/2008 Higham et al.
7,357,798 B2 4/2008 Sharps et al.
7,377,942 B2 5/2008 Berry
7,682,540 B2 3/2010 Boyan et al.
7,828,853 B2 11/2010 Ek et al.
7,910,124 B2 3/2011 Boyan et al.
8,002,830 B2 8/2011 Boyan et al.
8,142,808 B2 3/2012 Boyan et al.
8,318,192 B2 11/2012 Boyan et al.
2001/0029399 A1 10/2001 Ku
2001/0038831 A1 11/2001 Park et al.
2001/0046488 A1 11/2001 Vandenburgh et al.
2002/0026244 A1 2/2002 Trieu
2002/0031500 A1 3/2002 MacLaughlin et al.
2002/0034646 A1 3/2002 Canham
2002/0072116 A1 6/2002 Bhatia et al.
2002/0140137 A1 10/2002 Sapieszko et al.
2002/0173855 A1 11/2002 Mansmann
2002/0183845 A1 12/2002 Mansmann
2002/0183848 A1 12/2002 Ray et al.
2002/0187182 A1 12/2002 Kramer et al.
2003/0008395 A1 1/2003 Holy et al.
2003/0008396 A1 1/2003 Ku
2003/0021823 A1 1/2003 Landers et al.
2003/0055505 A1 3/2003 Sicotte et al.
2003/0059463 A1 3/2003 Lahtinen
2003/0082808 A1 5/2003 Guan et al.
2003/0175656 A1 9/2003 Livne et al.
2003/0176922 A1 9/2003 Lawson et al.
2003/0199984 A1 10/2003 Trieu
2003/0220695 A1 11/2003 Sevrain
2003/0233150 A1 12/2003 Bourne et al.
2004/0010048 A1 1/2004 Evans et al.
2004/0024465 A1 2/2004 Lambrecht et al.
2004/0044412 A1 3/2004 Lambrecht et al.
2004/0052867 A1 3/2004 Canham
2004/0059415 A1 3/2004 Schmieding
2004/0059425 A1 3/2004 Schmieding
2004/0063200 A1 4/2004 Chaikof et al.
2004/0064195 A1 4/2004 Herr
2004/0073312 A1 4/2004 Eisermann et al.
2004/0092653 A1 5/2004 Ruberti et al.
2004/0117022 A1 6/2004 Marnay et al.
2004/0143327 A1 7/2004 Ku
2004/0143329 A1 7/2004 Ku
2004/0143333 A1 7/2004 Bain et al.
2004/0147016 A1 7/2004 Rowley et al.
2004/0171143 A1 9/2004 Chin et al.
2004/0172135 A1 9/2004 Mitchell
2004/0220296 A1 11/2004 Lowman et al.
2004/0220669 A1 11/2004 Studer
2004/0220670 A1 11/2004 Eisermann et al.
2004/0249465 A1 12/2004 Ferree
2005/0037052 A1 2/2005 Udipi et al.
2005/0043733 A1 2/2005 Eisermann et al.
2005/0043802 A1 2/2005 Eisermann et al.
2005/0049706 A1 3/2005 Brodke et al.
2005/0055094 A1 3/2005 Kuslich
2005/0055099 A1 3/2005 Ku
2005/0071003 A1 3/2005 Ku
2005/0074877 A1 4/2005 Mao
2005/0079200 A1 4/2005 Rathenow et al.
2005/0090901 A1 4/2005 Studer
2005/0096744 A1 5/2005 Trieu et al.
2005/0106255 A1 5/2005 Ku
2005/0137677 A1 6/2005 Rush
2005/0137707 A1 6/2005 Malek
2005/0143826 A1 6/2005 Zucherman et al.
2005/0149196 A1 7/2005 Zucherman et al.
2005/0154462 A1 7/2005 Zucherman et al.
2005/0154463 A1 7/2005 Trieu
2005/0169963 A1 8/2005 Van Dyke et al.
2005/0171608 A1 8/2005 Peterman et al.
2005/0177238 A1 8/2005 Khandkar et al.
2005/0209704 A1 9/2005 Maspero et al.
2005/0216087 A1 9/2005 Zucherman et al.
2005/0228500 A1 10/2005 Kim et al.
2005/0233454 A1 10/2005 Nies et al.
2005/0244449 A1 11/2005 Sayer et al.
2005/0260178 A1 11/2005 Vandenburgh et al.
2005/0261682 A1 11/2005 Ferree
2005/0273176 A1 12/2005 Ely et al.
2005/0277921 A1 12/2005 Eisermann et al.
2005/0278025 A1 12/2005 Ku et al.
2005/0287187 A1 12/2005 Mansmann
2006/0002890 A1 1/2006 Hersel et al.
2006/0052874 A1 3/2006 Johnson et al.
2006/0052875 A1 3/2006 Bernero et al.
2006/0052878 A1 3/2006 Schmieding
2006/0058413 A1 3/2006 Leistner et al.
2006/0064172 A1 3/2006 Trieu
2006/0064173 A1 3/2006 Guederian
2006/0083728 A1 4/2006 Kusanagi et al.
2006/0100304 A1 5/2006 Vresilovic et al.
2006/0121609 A1 6/2006 Yannas et al.
2006/0122706 A1 6/2006 Lo
2006/0136064 A1 6/2006 Sherman

(56) **References Cited**

U.S. PATENT DOCUMENTS

2006/0136065	A1	6/2006	Gontarz et al.
2006/0200250	A1	9/2006	Ku
2006/0206209	A1	9/2006	Cragg et al.
2006/0224244	A1	10/2006	Thomas et al.
2006/0229721	A1	10/2006	Ku
2006/0235541	A1	10/2006	Hodorek
2006/0257560	A1	11/2006	Barone et al.
2006/0259144	A1	11/2006	Trieu
2006/0282165	A1	12/2006	Pisharodi
2006/0282166	A1	12/2006	Molz et al.
2006/0287730	A1	12/2006	Segal et al.
2006/0293561	A1	12/2006	Abay
2006/0293751	A1	12/2006	Lotz et al.
2007/0010889	A1	1/2007	Francis
2007/0014867	A1	1/2007	Kusanagi et al.
2007/0032873	A1	2/2007	Pisharodi
2007/0038301	A1	2/2007	Hudgins
2007/0043441	A1	2/2007	Pisharodi
2007/0067036	A1	3/2007	Hudgins et al.
2007/0073402	A1	3/2007	Vresilovic et al.
2007/0093906	A1	4/2007	Hudgins et al.
2007/0106387	A1	5/2007	Marcolongo et al.
2007/0116678	A1	5/2007	Sung et al.
2007/0118218	A1	5/2007	Hooper
2007/0118225	A1	5/2007	Hestad et al.
2007/0134333	A1	6/2007	Thomas et al.
2007/0135922	A1	6/2007	Trieu
2007/0142326	A1	6/2007	Shue
2007/0162135	A1	7/2007	Segal et al.
2007/0164464	A1	7/2007	Ku
2007/0167541	A1	7/2007	Ruberti et al.
2007/0168039	A1	7/2007	Trieu
2007/0173951	A1	7/2007	Wijlaars et al.
2007/0179606	A1	8/2007	Huyghe et al.
2007/0179614	A1	8/2007	Heinz et al.
2007/0179615	A1	8/2007	Heinz et al.
2007/0179617	A1	8/2007	Brown et al.
2007/0179618	A1	8/2007	Trieu et al.
2007/0179620	A1	8/2007	Seaton, Jr. et al.
2007/0179621	A1	8/2007	McClellan, III et al.
2007/0179622	A1	8/2007	Denoziere et al.
2007/0196454	A1	8/2007	Stockman et al.
2007/0202074	A1	8/2007	Shalaby
2007/0203095	A1	8/2007	Sadozai et al.
2007/0203580	A1	8/2007	Yeh
2007/0208426	A1	9/2007	Trieu
2007/0213718	A1	9/2007	Trieu
2007/0213822	A1	9/2007	Trieu
2007/0213823	A1	9/2007	Trieu
2007/0213824	A1	9/2007	Trieu
2007/0213825	A1	9/2007	Thramann
2007/0224238	A1	9/2007	Mansmann et al.
2007/0225823	A1	9/2007	Hawkins et al.
2007/0227547	A1	10/2007	Trieu
2007/0233259	A1	10/2007	Muhanna et al.
2007/0265626	A1	11/2007	Seme
2007/0270876	A1	11/2007	Kuo et al.
2007/0270970	A1	11/2007	Trieu
2007/0270971	A1	11/2007	Trieu et al.
2007/0299540	A1	12/2007	Ku
2008/0004707	A1	1/2008	Cragg et al.
2008/0015697	A1	1/2008	McLeod et al.
2008/0021563	A1	1/2008	Chudzik
2008/0031962	A1	2/2008	Boyan et al.
2008/0045949	A1	2/2008	Hunt et al.
2008/0051889	A1	2/2008	Hodorek
2008/0057128	A1	3/2008	Li et al.
2008/0075657	A1	3/2008	Abrahams et al.
2008/0077242	A1	3/2008	Reo et al.
2008/0077244	A1	3/2008	Robinson
2008/0097606	A1	4/2008	Cragg et al.
2008/0103599	A1	5/2008	Kim et al.
2008/0114367	A1	5/2008	Meyer
2008/0125870	A1	5/2008	Carmichael et al.
2008/0131425	A1	6/2008	Garcia et al.
2008/0145404	A1	6/2008	Hill et al.
2008/0154372	A1	6/2008	Peckham
2008/0166329	A1	7/2008	Sung et al.
2008/0279941	A1	11/2008	Boyan et al.
2008/0279943	A1	11/2008	Boyan et al.
2009/0182421	A1	7/2009	Silvestrini et al.
2009/0263446	A1	10/2009	Boyan et al.
2010/0198258	A1	8/2010	Heaven et al.
2011/0040332	A1	2/2011	Culbert et al.
2011/0172771	A1	7/2011	Boyan et al.

FOREIGN PATENT DOCUMENTS

EP	0222407	A2	5/1987
EP	0346129	A1	12/1989
EP	0505634	A1	9/1992
EP	0410010	B1	10/1993
EP	0411105	B1	6/1995
EP	0845480	A1	6/1998
EP	0919209	A1	6/1999
EP	1287796	A1	3/2003
EP	1030697	B1	8/2003
EP	1344538	A1	9/2003
EP	1584338	A2	10/2005
EP	1482996	B1	11/2005
GB	02056882	A	3/1981
GB	02128501	A	5/1984
JP	02-184580		7/1990
JP	04053843		2/1992
JP	07247365		9/1995
JP	11035732		2/1999
JP	2005-199054		7/2005
JP	2006-101893		4/2006
WO	WO90/07545	A2	7/1990
WO	WO90/07575	A1	7/1990
WO	WO90/10018	A1	9/1990
WO	WO93/16664	A1	9/1993
WO	WO94/01483	A1	1/1994
WO	WO95/25183	A1	9/1995
WO	WO97/06101	A1	2/1997
WO	WO97/46178	A1	12/1997
WO	WO98/02146	A2	1/1998
WO	WO98/50017	A1	11/1998
WO	WO99/25391	A2	5/1999
WO	WO99/34845	A1	7/1999
WO	WO00/30998	A1	6/2000
WO	WO00/42991	A1	7/2000
WO	WO00/62829	A1	10/2000
WO	WO00/66191		11/2000
WO	WO01/02033	A1	1/2001
WO	WO01/22902	A2	4/2001
WO	WO01/59160	A1	8/2001
WO	WO01/64030	A1	9/2001
WO	WO01/70436	A1	9/2001
WO	WO01/91822	A1	12/2001
WO	WO02/09647	A2	2/2002
WO	WO02/30480	A1	4/2002
WO	WO02/064182	A3	8/2002
WO	WO03/030787	A1	4/2003
WO	WO03/092760	A1	11/2003
WO	WO2004/060554	A1	7/2004
WO	WO2004/101013	A1	11/2004
WO	WO2005/077013	A2	8/2005
WO	WO2005/077304	A1	8/2005
WO	WO2005/097006	A2	10/2005
WO	WO2006/018531	A2	2/2006
WO	WO2006/019634	A1	2/2006
WO	WO2006/030054	A1	3/2006
WO	WO2006/034365	A2	3/2006

OTHER PUBLICATIONS

International Search Report for Application No. PCT/US2005/004045 mailed Jul. 15, 2005 (PCT/US2005/004045 is the corresponding PCT application of U.S. Appl. No. 11/053,409).

Andrade et al., "Water as a Biomaterial," Trans. Am. Soc. Artif. Intern. Organs, 19:1 (1973).

(56) **References Cited**

OTHER PUBLICATIONS

Ariga et al., "Immobilization of Microorganisms with PVA Hardened by Iterative Freezing and Thawing," Journal of Fermentation Technology, 65(6): pp. 651-658 (1987).

Boyan et al., "Effect of Titanium Surface Characteristics on Chondrocytes and Osteoblasts in Vitro," Cells and Materials, vol. 5, No. 4, pp. 323-335 (1995).

Boyan et al., "Osteoblast-Mediated Mineral Deposition in Culture is Dependent on Surface Microtopography," Calcif. Tissue Int., 71:519-529 (2002).

Brunette, "The Effects of Implant Surface Topography on the Behavior of Cells," Int. J. Oral Maxillofac Implants, 3:231-240 (1988).

Chen et al., "Boundary layer infusion of heparin prevents thrombosis and reduces neointimal hyperplasia in venous polytetrafluoroethylene grafts without system anticoagulation," J. Vascular Surgery, 22:237-247 (1995).

Chu et al., "Polyvinyl Alcohol Cryogel: An Ideal Phantom Material for MR Studies of Arterial Elasticity," Magnetic Resonance in Medicine, v. 37, pp. 314-319 (1997).

Hickey et al., "Mesh size and diffusive characteristics of semicrystalline poly(vinyl alcohol) membranes prepared by freezing/thawing techniques," Journal of Membrane Science, 107(3), pp. 229-237 (1995).

Hoffman et al., "Interactions of Blood and Blood Components at Hydrogel Interfaces," Ann. New York Acad. Sci., 283:372-382 (1977).

Hunt, Knee Simulation, Creep, and Friction Tests of Poly(Vinyl Alcohol) Hydrogels Manufactured Using Injection Molding and Solution Casting, Thesis for M.S., University of Notre Dame (Jul. 2006).

Katta et al., "Friction and wear behavior of poly(vinyl alcohol)/poly(vinyl pyrrolidone) hydrogels for articular cartilage replacement," Journal of Biomedical Materials Research, vol. 83A, pp. 471-479 (2007).

Kieswetter et al., "The Role of Implant Surface Characteristics in the Healing of Bone," Crit. Rev. Oral Biol. Med., 7(4):329-345 (1996).

Kieswetter et al., "Surface roughness modulates the local production of growth factors and cytokines by osteoblast-like MG-63 cells," Journal of Biomedical Materials Research, vol. 32, pp. 55-63 (1996).

Kobayashi et al., "Characterization of a polyvinyl alcohol-hydrogel artificial articular cartilage prepared by injection molding," J. Biomater. Sci. Polymer Edn., 15(6): 741-751 (2003).

Kobayashi et al., "Development of an artificial meniscus using polyvinyl alcohol-hydrogel for early return to, and continuance of, athletic life in sportspersons with severe meniscus injury. I: mechanical evaluation." The Knee, 10 (2003); 47-51.

Kohavi et al., "Markers of primary mineralization are correlated with bone-bonding ability of titanium or stainless steel in vivo," Clin. Oral. Impl. Res., 6:1-13 (1995).

Koutsopoulos et al., "Calcification of porcine and human cardiac valves: testing of various inhibitors for antimineralization," J. Mater. Sci. Mater. Med., 9:421-424 (1998).

Kwak, BK, et al., "Chitin-based Embolic Materials in the Renal Artery of Rabbits: Pathologic Evaluation of an Absorbable Particulate Agent", Radiology, 236:151-158 (2005).

Landolt et al., "Electrochemical micromachining, polishing and surface structuring of metals: fundamental aspects and new developments", Elsevier Science Ltd., pp. 3185-3201 (2003).

Lazzeri et al., "Physico-chemical and mechanical characterization of hydrogels of poly(vinyl alcohol) and hyaluronic acid," J. Mater. Sci. In Med., 5:862-867 (1994).

Liao et al., "Response of rat osteoblast-like cells to microstructured model surfaces in vitro," Biomaterials, 24, pp. 649-654 (2003).

Lozinsky et al., "Study of cryostructurization of polymer systems. VII. Structure formation under freezing of poly(vinyl alcohol) acqueous solutions," Colloid & Polymer Science, vol. 264, pp. 19-24 (1986).

Lozinsky et al., "Study of Cryostructuration of Polymer Systems. XII. Poly(vinyl alcohol) Cryogels: Influence of Low-Molecular Electrolytes," Journal of Applied Polymer Science, vol. 61, pp. 1991-1998 (1996).

Lozinsky et al., "Study of Cryostructuration of Polymer Systems. XI. The Formation of PVA Cryogels by Freezing-Thawing the Polymer Aqueous Solutions Containing Additives of Some Polyols," Journal of Applied Polymer Science, vol. 58, pp. 171-177 (1995).

Lozinsky et al., "Poly(vinyl alcohol) cryogels employed as matrices for cell immobilization. 2. Entrapped cells resemble porous fillers in their effects on the properties of PVA-cryogel carrier," Enzyme and Microbial Technology, vol. 20, No. 3, pp. 182-190 (1997).

Lozinsky et al., "Poly(vinyl alcohol) cryogels employed as matrices for cell immobilization. 3. Overview of recent research and developments," Enzyme and Microbial Technology, vol. 23, No. 3-4, pp. 227-242 (1998).

Lusta et al., "Immobilization of fungus *Aspergillus* sp. by a novel cryogel technique for production of extracellular hydrolytic enzymes", Process Biochemistry, vol. 35, pp. 1177-1182 (2000).

Ma et al., "Friction Properties of novel PVP/PVA blend hydrogels as artificial cartilage," Journal of Biomedical Materials Research, vol. 93A, pp. 1016-1019 (2010).

Martin et al., "Effect of titanium surface roughness on proliferation, differentiation, and protein synthesis of human osteoblast-like cells (MG63)," Journal of Biomedical Materials Research, vol. 29, pp. 389-401 (1995).

Nagura et al., "Structure of poly(vinyl alcohol) hydrogel prepared by repeated freezing and melting," Polymer, 30:762-765 (1989).

Nakashima et al., "Study on Wear Reduction Mechanisms of Artificial Cartilage by Synergistic Protein Boundary Film Formation," Japan Soc'y of Mech. Eng'r Int'l J., Series C, vol. 48, No. 4, pp. 555-561 (2005).

Oka et al., "Development of an Artificial Articular Cartilage", Clinical Materials, vol. 6, pp. 361-381 (1990).

Ong et al., "Osteoblast Responses to BMP-2-Treated Titanium In Vitro," The International Journal of Oral & Maxillofacial Implants, vol. 12, No. 5, pp. 649-654 (1997).

Peppas et al., "Reinforced uncrosslinked poly(vinyl alcohol) gels produced by cyclic freezing-thawing processes: a short review," Journal of Controlled Release, 16(3): 305-310 (1991).

Peppas et al., "Structure of Hydrogels by Freezing-Thawing Cyclic Processing," Bulletin of the American Physical Society, 36:582 (1991).

Peppas et al., "Controlled release from poly(vinyl alcohol) gels prepared by freezing-thawing processes," Journal of Controlled Release, vol. 18, pp. 95-100 (1992).

Peppas et al., "Ultrapure poly(vinyl alcohol) hydrogels with mucoadhesive drug delivery characteristics," European Journal of Pharmaceutics and Biopharmaceutics, 43(1): 51-58 (1997).

Ratner et al., Biomaterials Science An Introduction to Materials in Medicine, Academic Press, pp. 52, 53, & 62 (1996).

Ricciardi et al., "Structure and Properties of Poly(vinyl alcohol) Hydrogels Obtained by Freeze/Thaw Techniques," Macromol. Symp., 222: 49-63 (2005).

Schwartz et al., "Underlying Mechanisms at the Bone-Biomaterial Interface," Journal of Cellular Biochemistry, 56:340-347 (1994).

Singh et al., "Polymeric Hydrogels: Preparation and Biomedical Applications," J. Sci. Ind. Res., 39:162-171 (1980).

Stauffer et al., "Poly(vinyl alcohol) hydrogels prepared by freezing-thawing cyclic processing," Polymer 33(1818):3932-3936 (1992).

Stewart et al., "Protein release from PVA gels prepared by freezing and thawing techniques," Proc. Int. Symp. Controlled Release Bioact. Mater., 26th, 1004-1005 (1999).

Szczesna-Antezak et al., "*Bacillus subtilis* cells immobilised in PVA-cryogels," Biomolecular Engineering, vol. 17, pp. 55-63 (2001).

The American Heritage® Science Dictionary [online], Houghton Mifflin Company, 2002 [retrieved on Jun. 3, 2008]. Retrieved from the internet: <URL: http://dictionary.reference.com/browse/pore>.

Watase et al., "Rheological and DSC Changes in Poly(vinyl alcohol) Gels Induced by Immersion in Water," Journal of Polymer Science, Polym. Phys. Ed, 23(9): 1803-1811 (1985).

(56) **References Cited**

OTHER PUBLICATIONS

Watase et al., "Thermal and rheological properties of poly(vinyl alcohol) hydrogels prepared by repeated cycles of freezing and thawing," Makromol. Chem., v. 189, pp. 871-880 (1988).

Willcox et al., "Microstructure of Poly(vinyl alcohol) Hydrogels Produced by Freeze/Thaw Cycling," Journal of Polymer Sciences: Part B: Polymer Physics, vol. 37, pp. 3438-3454 (1999).

WordNet® 3.0 [online], Princeton University, 2006 [retrieved on Aug. 6, 2008]. Retrieved from the Internet: <URL: http://dictionary.reference.com/browse/mesh>.

Yamaura et al., "Properties of Gels Obtained by Freezing/Thawing of Poly(vinyl Alcohol)/Water/Dimethyl Sulfoxide Solutions," J. Appl. Polymer Sci., 37:2709-2718 (1989).

Yokoyama et al., "Morphology and structure of highly elastic poly-(vinyl alcohol) hydrogel prepared by repeated freezing-and-melting", Colloid & Polymer Science, vol. 264, No. 7, pp. 595-601 (1986).

Zheng-Qiu et al., "The development of artificial articular cartilage—PVA-hydrogel," Bio-Medical Materials and Engineering, vol. 8, pp. 75-81 (1998).

Bray et al., Poly(vinyl alcohol) Hydrogels for Synthetic Articular Cartilage Material, M. Biomed. Mater. Res., vol. 7, pp. 431-443.

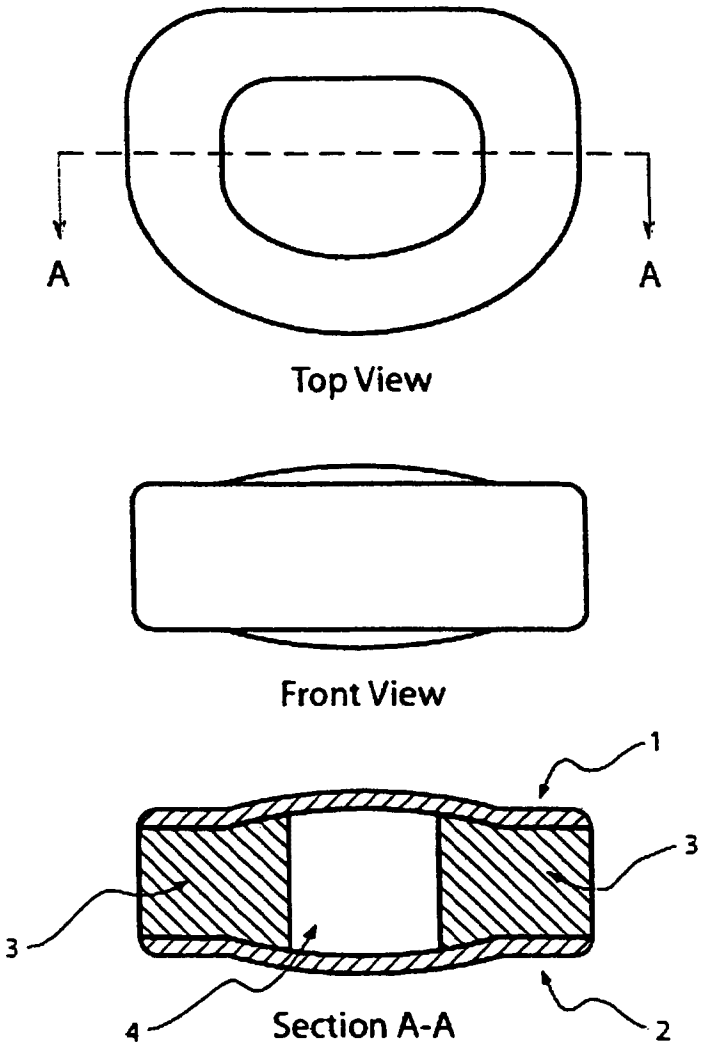
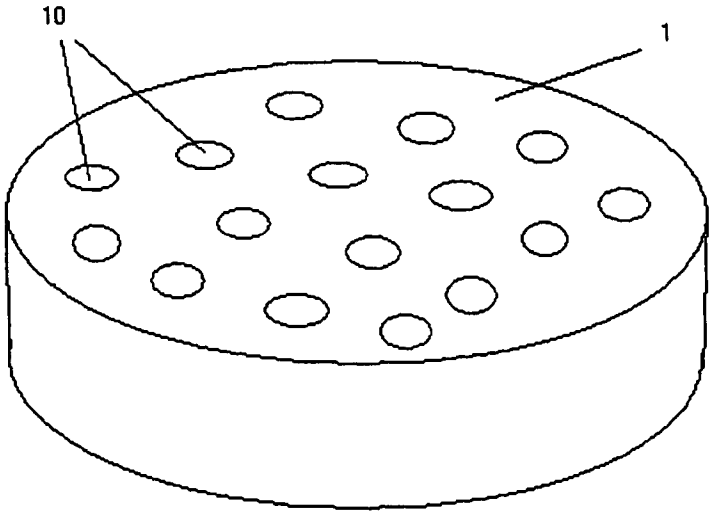


Figure 1

Figure 2



HYDROGEL IMPLANT WITH SUPERFICIAL PORES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 11/053,409, filed Feb. 7, 2005, which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/542,389, filed Feb. 6, 2004, both of which are incorporated by reference herein in their entireties.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to spinal disc replacement devices, particularly devices which mimic native spinal discs, for implantation which is compatible with living tissue. The invention also relates to implants suitable for load-bearing surfaces in the repair of tissue, replacement or augmentation, and methods of using such. One embodiment of the invention relates to an implantable spinal disc prosthesis.

2. Background Art

Materials used in the construction of implantable medical devices must be nontoxic, nonantigenic, and noninflammatory. Hydrogels are a preferred type of polymeric material for implantable devices. Because of their high water content, analogous to living tissue, they are superior in biocompatibility to non-hydrous polymeric materials.

U.S. Pat. No. 5,981,826, issued to Ku et al., describes the preparation of polyvinyl alcohol hydrogels (PVA-H) by physically crosslinking an aqueous solution of polyvinyl alcohol (PVA) to produce a gel. The crosslinking is accomplished by subjecting the aqueous PVA solution to multiple cycles of freezing and thawing. One limitation of the prior art is that the hydrogels produced are relatively nonporous and the pore size and degree of porosity, that is the density of the pores within the hydrogel, cannot vary independently of the mechanical properties or stiffness of the hydrogel.

Methods for producing certain porous hydrogels also exist in the art. U.S. Pat. No. 6,268,405, issued to Yao et al., describes methods for creating porous PVA-Hs by including immiscible materials in the polymerization process. After the hydrogel is polymerized, the included immiscible materials are washed out of the hydrogel by an appropriate solvent, yielding pores which are broadly distributed throughout the hydrogel. Controlling the size and density of the pores is accomplished by varying the molecular weight of the immiscible materials. A disadvantage of Yao et al. is that the range of attainable pore sizes is limited. Moreover, the invention of Yao et al. is limited in that it can only produce hydrogels whose pores extend throughout the hydrogel. The pores in Yao et al. are intended to create vascularization of the hydrogel in soft or non-load bearing tissue. A further disadvantage of Yao et al. is that the pore sizes are broadly distributed about the average pore size.

Artificial discs intended for the replacement of a damaged intravertebral disc have been described. These are typically articulated devices comprising two rigid metal plates adhered to opposite ends of an elastomeric core. In use, the artificial disc is placed in the intervertebral space and the metal plates are secured to the surfaces of adjacent vertebrae. Various embodiments of artificial discs of this type are described in U.S. Pat. Nos. 5,674,296 and 6,156,067, issued to Bryan et al., U.S. Pat. No. 5,824,094, issued to Serhan et al., U.S. Pat. No. 6,402,785, issued to Zdeblick et al. More recent embodiments, e.g. U.S. Pat. No. 6,419,704, issued to Ferree and U.S. Pat. No. 6,482,234, issued to Weber et al., include descriptions of elastomeric cores that may be formed from materials with different elasticities to better mimic the native structure of spinal discs.

Artificial discs have also been described wherein the disc is comprised of a flexible urethane silicone blend core and two identical rigid surfaces on either side of the core. U.S. Pat. No. 6,607,558 to Kuras describes such a disc where nail like projections extend from the surface to fixate the disc between the vertebrae. Such a disc also possesses a different material for the end plates as for the elastic core.

The disadvantage of the artificial disc devices of the prior art are numerous. These prior art devices require the mechanical attachment of rigid artificial materials, such as titanium, directly to the bone with screws, staples, nails, cement, or other mechanical means. These rigid materials are only minimally compatible with natural, living bone and separation of the implant from the bone is often observed over long-term implantation. In addition, materials used in artificial discs of the prior art have physical and mechanical properties distinctly different from those of natural spinal discs and thus inadequately duplicate the desired properties of native spinal discs.

Vertebral fusion is still the most commonly performed procedure to treat debilitating pain associated with degenerative spinal disc disease or disc trauma, despite the fact that the procedure has many drawbacks. Vertebral fusion increases stress and strain on the discs adjacent to the fusion site, and it is now widely accepted that fusion is responsible for the accelerated degeneration of adjacent levels. Current multi-component spinal disc prosthesis designs, elastomeric cores with metal plates on both the upper and lower surfaces, are susceptible to problems with interfacial bonding and wear. These designs have shown spontaneous device detachment due to retraction of bone tissue from the metal surface.

Bone ingrowth and attachment in the art has often required the use of bone promoting growth factors. For example, U.S. Pat. No. 5,108,436, issued to Chu et al., describes using a porous implant for use in load bearing bone replacement which is used in combination with an osteogenic factor such as TGF-β.

Biomedical devices which are implanted in or around bone often fail because of fibrinogen encapsulation of the implant instead of cellular attachment to the implant itself. This encapsulation is a defensive reaction attempting to minimize contact between the body and the implant and is considered a sign of implant incompatibility.

Moreover, the art of bone ingrowth onto implantable surface contains a multitude of examples relating to porous directed ingrowth where bone essentially grows into and around channels of the implant. For example, U.S. Pat. No. 4,911,720, issued to Collier et al., discusses the ingrowth of bone into interconnecting pores which essentially locks bone into place. This method is disadvantageous in that bone does not actually attach itself to the material, instead bone attaches to other bone around the implant. In the unfortunate event that an implant must be removed, this type of Collier ingrowth results in large amounts of disruption to the surrounding bone tissue.

SUMMARY OF THE INVENTION

The present invention describes a hydrogel for implantation into a load bearing space within the body. The hydrogel has a textured surface on it which is comprised of superficial surface pores. Stated differently, the pores on the surface of the hydrogel substrate do not extend throughout the hydrogel

but instead remain within a region near the surface. The pores on this hydrogel substrate can have an average diameter of between 1 and 100 micrometers. Preferably the average diameter of surface pores on the hydrogel substrate is between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The superficial pores of this hydrogel substrate can vary in size by less than 50%, preferably less than 30%, and preferably less than 10%. The hydrogel substrate of the present invention can be made up of polyvinyl alcohol and can have a water content of at least 5% w/w of the overall hydrogel. The hydrogel substrate of the present invention could be used in any load bearing implantable device application including, but not limited to, a spinal disc replacement. The present invention when used as a spinal disc replacement can possess the surface pores in the proper configuration and be additionally comprised of multiple regions of varying elasticities. It is also possible that the regions of varying elasticities of the spinal disc replacement be comprised of multiple hydrogels as opposed to one hydrogel of varying elasticities.

The present invention also includes a method for making a hydrogel substrate with a textured surface for use in a load bearing biocompatible device. The hydrogel in liquid form is exposed to solid objects or to a mold which when polymerized or hardened results in a hydrogel with a textured surface. The solid objects used to impart the superficial pores may be made of polystyrene beads. Also, the solid objects used to impart the superficial pores may be grit, sand, silicon, silica, and ultra-fine particulate matter. The solid objects used to create the superficial pores can have a diameter of between 1 and 100 micrometers, preferably between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The solid objects used to create the superficial pores of this invention can be removed, for example, by use of an organic solvent or other washing means. This hydrogel substrate can be comprised of poly-vinyl alcohol possessing a water content of at least 5% w/w of the overall hydrogel.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is an elevation view of spinal disc replacement made in accordance with one embodiment of the present invention.

FIG. **2** is a schematic of a surface generated in accordance with one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is drawn to an implantable hydrogel substrate comprising a hydrogel surface having a plurality of superficial pores thereon. The pores on this hydrogel substrate can have an average diameter of between 1 and 100 micrometers. Preferably the average diameter of surface pores on the this hydrogel substrate is between 5 and 50 micrometers, and preferably between 10 and 30 micrometers. The superficial pores of this hydrogel substrate can vary in size by less than 50%, preferably less than 30%, and preferably by less than 10%. The hydrogel substrate of the present invention can be made up of polyvinyl alcohol and can have a water content of at least 5% w/w of the overall hydrogel.

One embodiment of the present invention is an artificial disc for implantation into the spine comprising the hydrogel substrate described above. This artificial disc is a hydrogel possessing a plurality of regions having variable elasticity. Specifically, the disc is comprised of a surface region having a higher modulus of elasticity than an interior region. This disc can be prepared using multiple hydrogels with the elastic properties of the one disc with varying regions of elasticity.

The present invention also includes a method for making a hydrogel substrate comprising contacting solid objects with an aqueous hydrogel, allowing the hydrogel to polymerize and crosslink while the solid objects are at least partially immersed in the hydrogel, and removing those solid objects from the polymerized and crosslinked hydrogel to form superficial pores thereon. The solid objects used to impart the superficial pores may be polystyrene beads. Alternatively, the solid objects used to impart the superficial pores may be grit, sand, silicon, silica, and ultra-fine particulate matter. The solid objects used to create the superficial pores and therefore the pores themselves can have a diameter of between 1 and 100 micrometers, preferably between 5 and 50 micrometers, and preferably between 10 and 30 micrometers.

The solid objects used to create the superficial pores of this invention can be removed for example by use of an organic solvent or other washing means. This hydrogel substrate can be comprised of poly-vinyl alcohol possessing a water content of at least 5% w/w of the overall hydrogel.

Accordingly, the present invention is directed to an implantable hydrogel substrate product, a method of making that product, and a method of using that product which substantially improves upon the limitations existing in the art. To achieve these and other advantages in accordance with the purpose of the invention, as embodied and broadly described herein, the invention includes a load bearing biocompatible hydrogel for medical implantation that promotes bone attachment. The hydrogel substrate consists of a hydrogel surface component which has been optimized for implantation. This is accomplished through pores on the surface having a controlled range in distribution of size. The surface pores are superficial and do not extend throughout the hydrogel.

Hydrogels are materials whose state is between that of a solid and of a liquid. Gels consist of polymeric, i.e. long chain, molecules linked together to form a three-dimensional network and are embedded in a liquid medium. In the case of hydrogels, the liquid medium comprises water. The polymer backbone of hydrogels is formed by hydrophilic monomer units and may be neutral or ionic. Examples of neutral and hydrophilic monomer units are ethylene oxide, vinyl alcohol, (meth)acrylamide, N-alkylated(meth)acrylamides, N-methylol(meth)acrylamide, N-vinylamides, N-vinylformamide, N-vinylacetamide, N-vinyl-N-methylacetamide, N-vinyl-N-methylformamide, hydroxyalkyl(meth)acrylates such as hydroxyethylmethacrylate, vinylpyrrolidone, (meth)acrylic esters of polyethylene glycol monoallyl ethers, allyl ethers, of polyethylene glycols, and sugar units such as glucose or galactose. Examples of cationic hydrophilic monomer units are ethyleneimine (in the protonated form), diallyldimethylammonium chloride and trimethylammonium propylmethacrylamide chloride. Examples of anionic monomer units are (meth)acrylic acid, crotonic acid, maleic acid, fumaric acid, itaconic acid, 2-acrylamido-2-methylpropanesulfonic acid, vinylsulfonic acid, vinylphosphonic acid, 2-methacryloyloxyethanesulfonic acid, 4-vinylbenzenesulfonic acid, allylsulfonic acid, vinyltoluenesulfonic acid and vinylbenzenephosphonic acid.

From the example listing above, a hydrogel for use in the present invention may be selected based upon its biocompatibility and stability at various hydration states. For the purposes of the present invention, a suitable hydrogel will have a moisture content of at least 5% w/w of the overall hydrogel, preferably at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, or 80% w/w of the overall hydrogel.

Initial events following implantation of a biomaterial in an orthotopic surgical site include rapid adsorption of serum constituents onto the implant surface. The first cells that are

likely to come into contact with the surface are polymorphonuclear cells, platelets, monocytes, and macrophages. These cells release bioactive factors that promote mesenchyrnal cell migration to the wound site. In addition to these natural factors associated with wound healing, surgeons frequently use bone graft and bone graft substitutes to improve bone formation. Such materials include osteoinductive agents such as demineralized bone matrix and bone morphogenetic protein. If appropriate signals are present mesenchymal cells with an osteoprogenitor phenotype will continue to differentiate into osteoblasts; of these a subset will become osteocytes. Ultimately, the newly formed bone will be remodeled via osteoclastic resorption. The present invention also provides that well-known grafting agents may be incorporated into the hydrogel composition, which includes, but is not limited to growth factors, angiogenic agents, antibiotics, and the like.

Chemically modified or polar surfaces are generally known to be able to produce more reactive protein adsorption to the implant surface than unmodified or non-polar surfaces. The increased reactivity of the proteins adsorbed onto the polar surface is thought to promote cellular adhesion to that surface. Therefore, the invention provides that the hydrogel composition can possess chemically modified or polar surfaces.

In general, many materials are well-tolerated in bone, but the success of long-term or chronic implantation often depends on the intimacy of the interface between the material surface and the bone. Microarchitecture of the surface is an important determinant of cell response. It has been observed that osteoblast phenotypic expression is surface-dependent. As described herein, specific surface characteristics enhance osteoblast differentiation while permitting proliferation, leading to optimal cell response to the implantation.

The mechanical properties of the material must be appropriate for the application. When the mechanical properties of the material are similar to the mechanical properties of the tissue adjacent to the implant, tissue tolerance of the artificial material is enhanced. Polymeric and elastomeric biomaterials can be fabricated with a wide range of mechanical properties, making them suitable for many applications as implantable devices. Because of their high water content, similar to that of living tissue, hydrogels are superior in biocompatibility to non-hydrous polymeric materials. Poly-vinyl alcohol (PVA) is an example of a polymer that can be used to form hydrogels, and has been studied extensively for its potential in biomedical applications. Poly-vinyl alcohol hydrogels (PVA-Hs) are biologically well tolerated and compatible with living cartilage tissue.

PVA-Hs can be produced from solution via repeated freezing and thawing cycles that increase the order of the microcrystalline regions, changing the dissolution properties, mesh size, and diffusion properties of the polymer. Also, PVA-Hs can be produced from solution via a slow and sustained transition through the freezing point of the solution. The mechanical properties of PVA-Hs can be varied over a wide range, and stable PVA gels can easily be produced to have an elastic modulus ranging from a few MPa, such as articular cartilage, to about 50 MPa, such as the stiffest portion of the annulus of spinal discs.

Increasing the porosity of a hydrogel substrate produces decreased mechanical strength. When porous hydrogels are used to provide the requisite surface of the present invention, it is advantageous that the porosity not extend throughout the hydrogel, but be limited to a relatively shallow depth below the surface. The thickness of the porous portion of the hydrogel is preferably less than 1 millimeter, less than 500 micrometers, and most preferable less than or equal to 200 micrometers.

The hydrogel substrates of the present invention can be used for implantation into any part of the body. One embodiment of this invention is an artificial intervertebral disc, comprising one or more hydrogels shaped substantially similarly to a natural intervertebral disc. The upper and lower surfaces of the hydrogel, or assembly of hydrogels, are constructed to have a rouges or textured surface with a defined porosity. That porosity depends primarily upon the size of a solid object used to create the surface texture. The surface texture is created by the distribution of pores that do not continue throughout the hydrogel, or, in other words, the pores are superficial. The size of the pores can be from 2 to 100 micrometers, preferably from 5 to 50 micrometers, and preferably, from 10 to 30 micrometers.

The porosity of the hydrogel surface embodied in this invention may be realized in a variety of ways. Molds may be constructed with patterning on the appropriate surfaces of the cavities in the mold. Alternatively, the porosity may be produced by abrasion of a smooth hydrogel surface after molding. Abrading the surface with grit will result in a surface textured such as desired in this invention. Techniques for applying and using abrasives are well known to those of skill in the art.

One technique for producing the surface roughness of artificial discs of this invention involves providing solid objects having the size and shape of the required surface rugosity and then using these solid objects as a template for the construction of a mold. Alternatively, these solid objects may be embedded in the hydrogels of the present invention during the molding process and removed afterwards. Removal of the solid objects leaves behind on the surface of the hydrogel pores, cavities, and other invaginations required for the texture of the surface to be obtained.

One example of a material that can be used as solid objects to impart the surface texture on the hydrogels of the present invention is polystyrene. Polystyrene beads, commonly called latex beads, are commercially available in sizes ranging from 0.02 to 1000 micrometers, and can have a very narrow size distribution. Such a narrow size distribution is advantageous for applications requiring uniform surface roughness. For example, when using polystyrene beads with an average diameter of 20.3 μm an acceptable range for the distribution of bead size would be .+−.0.6 μm, preferably .+−.0.5 μm, and preferably .+−.0.4 μm. Polystyrene beads may be obtained having surface functional groups useful for covalent chemical attachment of various chemical entities to the surface of the beads. Polystyrene beads may also be obtained either crosslinked or uncrosslinked. The latter type of beads are insoluble in water, but freely soluble in many organic solvents. Thus, one method for removal of the beads after the molding process is the dissolution of the beads in appropriate organic solvents.

The pores on the textured surface in this embodiment enable the surface to resemble native bone which has undergone osteoclastic resorption. When surface textured hydrogels are used to provide the requisite surface porosity, it is advantageous for the pores not to extend throughout the hydrogel, but instead be limited to a relatively shallow depth below the textured surface. The thickness of the porous portion of the hydrogel surface is preferably less than 1 millimeter, preferably less than or equal to 500 micrometers, and preferably less than or equal to about 200 micrometers.

The hydrogels of the present invention may contain bioactive factors to further stimulate cell growth or differentiation.

These factors, for instance attachment peptides, such as RGD containing peptides, and growth factors such as bone morphogenic proteins, insulin-like growth factor, platelet derived growth factor, fibroblast growth factor, cartilage-derived growth factor, transforming growth factor-beta, and parathyroid hormone related peptide, as well as other regulatory chemicals such as statins, prostaglandins, and mineral ions well-known in the art. These factors may be included in the hydrogels of this invention singly or in combination, and they may be included with or without binding proteins.

The hydrogels of the present invention may also contain bone or cartilage forming cells (osteoblasts or chondrocytes) or precursor cells to bone and cartilage forming cells such as mesenchymal stem cells or osteoprogenitor cells. These precursor cells have the capacity to differentiate into bone and/or cartilage forming cells. Cells may be included in the hydrogels of the present invention alone or in combination with bioactive factors to further stimulate cell growth or differentiation.

Natural intervertebral discs have a tough outer fibrocartilaginous ring called the annulus fibrosus and a soft, inner, highly elastic structure called the nucleus pulpous. The artificial discs of the present invention may contain an inner core constructed to mimic the physical and mechanical properties of the natural nucleus pulpous, surrounded by an annular region constructed to mimic the physical and mechanical properties of the natural annulus fibrosus.

In one embodiment, these regions comprise hydrogels whose water content, degree of polymerization, and degree of crosslinking are adjusted to produce the requisite physical and mechanical properties. The hydrogel comprising the inner core has a higher water content and/or a lower degree of polymerization and/or a lower degree of crosslinking to produce a relatively soft and elastic hydrogel. The hydrogel comprising the outer annular region has a lower water content and/or a higher degree of polymerization and/or crosslinking to produce a relatively hard outer hydrogel which mechanically is tough and stiff. The hydrogels comprising the upper and lower surfaces may substantially resemble the hydrogel comprising the annular region in terms of physical and mechanical properties, water content, and degrees of crosslinking and polymerization. The additional requirement, however, for the surfaces to be porous may allow or require a different combination of physical and mechanical properties in these hydrogels compared to the hydrogel comprising the outer annular region.

FIG. **1** shows a spinal disc replacement envisioned by the present invention. The spinal disc has an upper portion **1** and a lower portion **2**. It is the hydrogel substrate surfaces of the upper portion **1** and lower portion **2** which possess the porous texture of the present invention. The upper portion **1** and lower portion **2** can be less elastic and more rigid than the inner region **4** which seeks to mimic the nucleus pulpous. Likewise, the spinal disc may have an intermediate region of elasticity **3** which further aids in the function of the spinal disc. The intermediate region of elasticity **3** may or may not differ from the elasticity of either the inner region **4** or the upper portion **1** or lower portion **2**.

FIG. **2** shows the upper portion **1** of the spinal disc of FIG. **1** possessing superficial surface pores **10** of the present invention. The sizing of these pores as described herein promotes differentiation of cells into desired tissues, such as bone or bone-like cells, and induces the attachment of those cells to the surface.

In one embodiment, the superficial pores can be created with solid polystyrene beads of 20.7 μm to 19.9 μm of average diameter suspended in the hydrogel solution, or coated on the appropriate surfaces of the mold prior to crosslinking of the hydrogel. After crosslinking, the polystyrene beads are removed by dissolving them in a solvent such as dimethyl formamide or its equivalent that does not dissolve the hydrogel. Such treatment produces porosity and surface roughness with dimensions approximately equal to the diameter of the polystyrene beads. The invaginations left behind after removal of the polystyrene beads contribute to the controlled surface texture desired in the present invention. The polystyrene beads of this embodiment may also be adhered to a surface and used as a part of a mold, or as a template in the construction of a mold.

In another embodiment of this invention, the solid object used in the casting of a rough hydrogel surface is grit. Grit can be any solid object that is small with a narrow size distribution. Examples of grit include sand, silica particles, silicone particles, metal shot, etc. Those skilled in the art would recognize the need to match the grit used to the hydrogel along with the method of removing the grit leaving the rough or porous surface.

A silica grit of appropriate size can be used to impart the proper level of porosity on the surface of a hydrogel. As was seen with the polystyrene, the sand is placed in the bottom of a mold and the aqueous hydrogel is poured into the mold. The hydrogel is allowed to crosslink and polymerize and is then removed from the mold. The hydrogel is then washed to remove the grit leaving behind the invaginations and pores which make up the textured surface of the hydrogel implant. Grit may also be adhered to a surface and used as a part of a mold, or as a template in the construction of a mold.

In yet another embodiment of the present invention, the mold used in the formation of the hydrogel substrate can be any type of material around which the hydrogel forms. For example, the mold can be a series of beads, grit, filter screens, mesh, wires, glass tubing, and the equivalents of these materials or items. Once the hydrogel has been allowed to form around the mold element, the mold is removed from the hydrogel manually, chemically, or any other means which will allow the hydrogel to remain intact once the mold has been removed.

In yet another embodiment of the present invention, the hydrogel substrate can be a load bearing patch which can be used in the repair of partially or predominately damaged tissue. For example, the hydrogel substrate bearing the textured surface of the present invention can be relatively thin and small in diameter. That hydrogel substrate can then be placed where deteriorated, either acutely or chronically, cartilage was removed.

In yet another embodiment of the present invention, the hydrogel substrate can be assembled outside the body in a malleable form. The malleable form of the hydrogel substrate can then be placed in the intended area, be it a spinal disc replacement, knee cartilage replacement, shoulder bursa repair, or other use one skilled in the art would foresee. Once in the proper position, the malleable hydrogel substrate could be hardened or polymerized via photopolymerization. Radiation curing or photopolymerization (photo-induced free radical polymerization) has become an important and useful technique for applying and curing coatings, inks and adhesives. Radiation-curable compositions typically comprise as essential components one or more radiation-curable monomers and a photoinitiator. The compositions are applied as a coating to various articles and surfaces and the monomers are polymerized to form a film by exposing the coating of the radiation-curable composition to radiation, typically ultraviolet (UV) or electron-beam radiation.

EXAMPLES

Example 1

Attachment of Polystyrene Objects to a Surface

To a suspension of carboxyl-modified polystyrene beads (20.3 μm.+−.0.43 μm diameter, Bangs Laboratories) in 20 nM MEW, pH 4.4 is added a 10-fold excess of water-soluble carbodiimide, 1-ethyl-3-(d-dimethylaminopropyl) carbodiimide hydrochloride. After 15 minutes at room temperature, the beads are washed twice by centrifugation and suspension in 20 mM HEPES, pH 7.5 and then resuspended in the same buffer. The resulting suspension is added to the wells of a 24-well tissue culture plate made of polycarbonate, having an amino-modified surface (Nalge Nunc International). After 60 minutes at room temperature, the unreacted beads are decanted, and the wells are washed gently with deionized water. Microscopic analysis shows the bottom surface of the wells are covered with a monolayer of polystyrene beads at a density of approximately 50%.

The surface with attached polystyrene objects of the previous example may be used as a template to fabricate a mold for providing the desired porous surface of the hydrogels of the present invention. This may be accomplished by making a metallic replica of a surface comprising a plurality of polystyrene objects using sputtering and/or metal plating techniques and the like, all of which are well known to those of skill in the art. The metallic replica thus produced may be replicated again and reinforced with further metal or other components, again using methods well known to those skilled in the art. The result is a mold suitable for producing the surface texture of the hydrogels of the present invention.

The polystyrene objects of the foregoing example may also be included in the hydrogels of the present invention during the molding process. Subsequent removal of the polystyrene objects provides the controlled surface porosity provided for the hydrogels of the present invention. This is illustrated in the following example.

Example 2

Construction of a PVA-H with Surface Topography for Implantation as a Spinal Disc Prosthesis

A two-part mold with inserts is used to produce the artificial disc depicted in FIG. **1**. The upper and lower halves of the mold are first separated to mold the upper and lower surface regions of the disc. The surface of each corresponding upper and lower surface is created by suspending in the aqueous hydrogel the objects for creating the superficial pores. That suspension is then poured into the well of a mold at a depth no greater than the desired depth of the superficial pores. That layer of hydrogel is allowed to polymerize and crosslink. From that base layer creating the outermost layer of the corresponding surface, the remainder of the bulk of the hydrogel substrate can be built up by adding additional depth of aqueous hydrogel.

A 30% w/w poly(vinyl alcohol) solution is prepared by mixing poly(vinyl alcohol) polymer (124,000-186,000 Av. MW, 99+% saponification, Aldrich Chemical Company) in sterile, deionized water. The polymer is dissolved by heating the mixture in an autoclave at 120° C. for 30 minutes. To a portion of the viscous liquid solution is added 30% w/w of the polystyrene objects from Example 1. This is mixed until a uniform suspension is obtained. To each of the cavities in each half of the mold is added a sufficient amount of this suspension to coat the surfaces of the mold cavities to a thickness of 200 μm. Inserts are placed in each cavity to spread the suspension across the surfaces of the cavities and maintain the 200 μm thickness.

The two halves of the mold are then subjected to five cycles of freezing and thawing. In each cycle, the molds are placed in a freezer at about −20° C. for approximately 12 hours then removed from the freezer and placed at room temperature for approximately 12 hours. The inserts defining the first 200 μm thickness of the top portion of the upper surface and the bottom portion of the lower surface are removed from the molds, and an additional amount of the 30% poly(vinyl alcohol) solution (without polystyrene objects) is added to the mold cavities. The amount added is sufficient to increase the thickness of the top portion of the upper surface and the bottom portion of the lower surface to 1 mm. Inserts are placed in each cavity to spread the solution and maintain the 1 mm thickness.

The two halves of the mold are subjected to five additional cycles of freezing and thawing as above. The inserts defining the top portion of the upper surface and the bottom portion of the lower surface are removed from the molds, and annular inserts defining the shape of the core region are placed in the cavities of the lower half of the mold. A 20% w/w poly(vinyl alcohol) solution is prepared by mixing poly(vinyl alcohol) polymer (89,000-98,000 Av. MW 99+% saponification, Aldrich Chemical Company) in sterile, deionized water and dissolving as above. The solution is filled into the annular inserts and the mold is subjected to five additional cycles of freezing and thawing. The annular inserts are removed, the two halves of the mold are assembled and clamped together, and the areas of the mold corresponding the annular region are filled with 30% poly(vinyl alcohol) solution. The assembled mold is subjected to five more cycles of freezing and thawing. The molded artificial discs are removed from the mold and immersed in dimethyl formamide to dissolve the included polystyrene objects, the rinsed three times with deionized water.

The artificial disc produced by the forgoing example has a soft and elastic inner core while the outer annular region and upper and lower surfaces are relatively hard, tough, and stiff. The surface of the artificial disc is smooth, except on the top portion of the upper surface and the bottom portion of the lower surface where the removal of the polystyrene objects produces a rough or rugose surface with a roughness of 20 μm. When artificial discs made according to this procedure are implanted into the intervertebral spaces of disectomized rabbits, extensive bone growth onto the surface occurs within 3 weeks.

Although the invention has been described with reference to a particular preferred embodiment with its constituent parts, features and the like, these are not intended to exhaust all possible arrangements, mechanical and electrical equivalents, or features, and indeed many other modifications and variations will be ascertainable to those of skill in the art.

What is claimed is:

1. A biocompatible hydrogel configured for implantation into a joint, comprising:

a top surface configured for attachment to a patient's native tissue;

a bottom surface generally opposite of the top surface;

a depth defined between the top surface and the bottom surface;

superficial pores located within about 1 millimeter of the top surface of the hydrogel;

wherein the superficial pores do not extend throughout an entire depth of the hydrogel;

wherein said superficial pores enhance osteoblast differentiation and permit proliferation of osteoblasts; and

wherein the hydrogel is load-bearing.

2. The biocompatible hydrogel of claim **1**, wherein the hydrogel is configured for implantation into at least one of a knee, shoulder or spine.

3. The biocompatible hydrogel of claim **1**, wherein the pores have an average cross-section of between about 1 to 100 micrometers.

4. The biocompatible hydrogel of claim **1**, wherein the pores have an average cross-section of between about 10 to 30 micrometers.

5. The biocompatible hydrogel of claim **1**, wherein the pores are within about 200 micrometers of the surface of the hydrogel.

6. The biocompatible hydrogel of claim **1**, wherein the hydrogel comprises polyvinyl alcohol.

7. The biocompatible hydrogel of claim **1**, wherein the hydrogel has a moisture content of at least 5% w/w of the overall hydrogel.

8. The biocompatible hydrogel of claim **1**, wherein the hydrogel has a moisture content of at least 30% w/w of the overall hydrogel.

9. The biocompatible hydrogel of claim **1**, wherein the hydrogel comprises a chemically-modified or polar surface to promote cellular adhesion.

10. A load bearing hydrogel implant comprising:

a first surface having a plurality of superficial pores thereon, said first surface being configured for attachment to a patient's native joint tissue;

wherein said superficial pores are located at or near the first surface;

wherein said superficial pores do not extend throughout said hydrogel;

wherein the hydrogel is configured for implantation into a joint;

wherein the superficial pores have an average cross-section of between about 1 and 100 micrometers; and

wherein the pores are within about 1 millimeter of the hydrogel surface.

11. The hydrogel implant of claim **10**, wherein the hydrogel is configured for implantation into at least one of a knee, shoulder or spine.

12. The hydrogel implant of claim **10**, wherein the pores have an average cross-section of between about 1 to 100 micrometers.

13. The hydrogel implant of claim **10**, wherein the pores have an average cross-section of between about 10 to 30 micrometers.

14. The hydrogel implant of claim **10**, wherein the pores are within about 1 millimeter of the surface of the hydrogel.

15. The hydrogel implant of claim **10**, wherein the pores are within about 200 micrometers of the surface of the hydrogel.

16. The hydrogel implant of claim **10**, wherein the hydrogel comprises polyvinyl alcohol.

17. The hydrogel implant of claim **10**, wherein the hydrogel has a moisture content of at least 5% w/w of the overall hydrogel.

18. The hydrogel implant of claim **10**, wherein the hydrogel has a moisture content of at least 30% w/w of the overall hydrogel.

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